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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,831	08/17/2006	Patrick Casara	SERVIER 503 PCT	2351

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EXAMINER	
SHIAO, REI TSANG	
ART UNIT	**PAPER NUMBER**
1626	

MAIL DATE	DELIVERY MODE
10/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,831	CASARA ET AL.	
	Examiner	Art Unit	
	REI-TSANG SHIAO	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/23/07, 8/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application claims benefit of the foreign application:

FRANCE 0401690 with a filing date 02/20/2004.

2. Claims 37-69 are pending in the application.

Information Disclosure Statement

3. Applicant's Information Disclosure Statements filed on August 17, 2006, and April 23, 2007 have been considered. Please refer to Applicant's copies of the 1449's submitted herein.

Responses to Election/Restriction

4. Applicant's election with traverse of election of Group I claims 37-69, in part, in the reply filed on July 23, 2008 is acknowledged. Election of a compound of Example 22, i.e., 4-(3-hexahydrocyclopenta[c]-pyrrol-2(1H)-ylpropoxy)benzamide, is also acknowledged. The traversal is on the grounds that a chemist would not find the instant invention to involve structurally distinct inventions. This is found not persuasive, and the reasons are given *infra*.

Claims 37-69 are pending in the application. The scope of the invention of the elected subject matter is as follows.

Claims 37-69, in part, drawn to compounds/compositions of formula (I), wherein the variable m, n, p or q independently represents an integer 1 thereof, the variables R1-R4 independently do <u>not</u> represent heteroaryl or heterocycloalkyl thereof, the

variables R1-R4 independently are not substituted with heteroaryl or heterocycloalkyl thereof, the variables R1-R2 or R2-R3 independently do not form heteroaryl or heterocycloalkyl group thereof, and their methods of use.

The claims 37-69 herein lack unity of invention under PCT rule 13.1 and 13.2 since the compounds defined in the claims lack a significant structural element qualifying as the special technical feature that defines a contribution over the prior art, see Svendsen et al. CAS: 109:210691. Svendsen et al. discloses similar isoquinoline or pyrrole compounds. Accordingly, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper. Furthermore, even if unity of invention under 37 CFR 1.475(a) is not lacking, which it is lacking, under 37 CFR 1.475(b) a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations:

(1) A product and a process specially adapted for the manufacture of said product', or

(2) A product and a process of use of said product; or

(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said process; or

(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

And, according to 37 CFR 1.475(c)

if an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b), unity of invention might not be present.

However, it is noted that unity of invention is considered lacking under 37 CFR 1.475(a) and (b). Therefore, since the claims are drawn to more than a product, and according to 37 CFR 1.475 (e)

> the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

The claims lack unity of invention and should be limited to only a product, or a process for the preparation, or a use of the said product. In the instant case, Groups I-II are drawn to various products, processes of making, and the final products do not contain a common technical feature or structure, and do not define a contribution over the prior art, i.e., similar isoquinoline or pyrrole compounds. Moreover, the examiner must perform a commercial database search on the subject matter of each group in addition to a paper search, which is quite burdensome to the examiner.

Claims 37-69, in part, embraced in above elected subject matter, are prosecuted in the case. Claims 37-69, in part, not embraced in above elected subject matter, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

The requirement is still deemed proper.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 68-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using compounds of formula (I) for increasing endogenous cerebral concentration of histamine (i.e., N^t-methylhistamine) in an animal model, it does not reasonably provide enablement for using compounds of the formula (I) for treating a condition selected from cognitive deficiencies (i.e., aging, mood disorders, Alzheimer's disease, Parkinson's disease, or Pick's diseases) in a patient(i.e., human). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case:

The nature of the invention

The nature of the invention of claims 68-69 is drawn to compounds with intent methods of use for treating a condition selected from cognitive deficiencies (i.e., aging, mood disorders, Alzheimer's disease, Parkinson's disease, or Pick's diseases).

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic or preventive regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833,166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Fang et al. US 7,034,182 disclose amine compounds of formula (I) for treating Alzheimer's disease by inhibiting a beta-secretase activity in a patient, see columns 75-80. Applicants are claiming compositions with intent methods of use using compounds of formula (I) effective to "treating a condition selected from cognitive deficiencies (i.e., aging, mood

disorders, Alzheimer's disease, Parkinson's disease, or Pick's diseases)" *in vivo*. As such, the specification fails to enable the skilled artisan to use the compounds of claims 68-69 effective to "treating a condition selected from cognitive deficiencies (i.e., aging, mood disorders, Alzheimer's disease, Parkinson's disease, or Pick's diseases)" *in vivo*.

In addition, there is no established correlation between *in vitro* activity and accomplishing treatment of "treating a condition selected from cognitive deficiencies (i.e., aging, mood disorders, Alzheimer's disease, Parkinson's disease, or Pick's diseases)", *in vivo*, and those skilled in the art would not accept allegations in the instant specification to be reliable predictors of success, and those skilled in the ad would not be able to use the compounds of the formula (I) since there is no description of an actual method wherein "treating a condition selected from cognitive deficiencies (i.e., aging, mood disorders, Alzheimer's disease, Parkinson's disease, or Pick's diseases)" *in vivo* in a host is treated.

Hence, one of skill in the art is unable to fully predict possible results from the administration of the compounds of claims 68-69 due to the unpredictability of the "treating a condition selected from cognitive deficiencies (i.e., aging, mood disorders, Alzheimer's disease, Parkinson's disease, or Pick's diseases)" *in vivo*. The "treating a condition selected from cognitive deficiencies (i.e., aging, mood disorders, Alzheimer's disease, Parkinson's disease, or Pick's diseases)" *in vivo* is known to have many obstacles that would prevent one of ordinary skill in the art from accepting treating or regimen on its face.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the listing of exemplary assay for increasing endogenous cerebral concentration of histamine (i.e., N^t-methylhistamine) in an animal model, see pages 47-49 of the specification. There are no *in vivo* working examples directly presenting for the treatment of cognitive deficiencies (i.e., aging, mood disorders, Alzheimer's disease, Parkinson's disease, or Pick's diseases) ameliorated by the administration of compounds of the instant invention.

The breadth of the claims

The breadth of the claims is compositions with intent methods of use of the instant compounds effective to "treating a condition selected from cognitive deficiencies (i.e., aging, mood disorders, Alzheimer's disease, Parkinson's disease, or Pick's diseases)" *in vivo*.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what "treating a condition selected from cognitive deficiencies (i.e., aging, mood disorders, Alzheimer's disease, Parkinson's disease, or Pick's diseases)" *in vivo* would be benefited (i.e., treated) by the administration of the instant compounds of the instant invention and would furthermore then have to determine which of the claimed methods of use would provide treatment of "treating a condition selected from cognitive deficiencies" *in vivo*, if any.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which methods of use exhibit the desired pharmacological activity and which diseases would benefit from this activity. Thus, the specification fails to provide sufficient support of the broad use of the pharmaceutical compounds of the instant claims 68-69 for the "treating a condition selected from cognitive deficiencies (i.e., aging, mood disorders, Alzheimer's disease, Parkinson's disease, or Pick's diseases)" *in vivo*. As a result necessitating one of skill to perform an exhaustive search for which "treating a condition selected from cognitive deficiencies (i.e., aging, mood disorders, Alzheimer's disease, Parkinson's disease, or Pick's diseases)" *in vivo*, can be treated by what pharmaceutical compounds of the instant claims in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

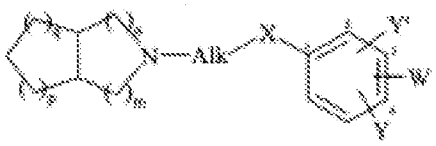
The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 37-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Svendsen et al. CAS: 109:210691.

Applicants claim compounds of formula (I), i.e.,



, wherein the variable m, n, p or q independently represents an integer from 0 to 2 thereof.

Determination of the scope and content of the prior art (MPEP §2141.01)

Svendsen et al. disclose a number of isoquinoline compounds, i.e., RN: 117262-99-4, 117263-07-7, 117263-09-9, 117429-42-2, 117429-43-3, or 117430-10-1.

Determination of the difference between the prior art and the claims (MPEP §2141.02)

The difference between instant claims and Svendsen et al. is that the instant the variable m, n, p or q of formula (I) independently represents an integer from 0 to 2 thereof, while Svendsen et al. represents 1 or, i.e., q is 1, p is 2, n is 2 and m is 1 at the same position. Svendsen et al. compounds inherently overlap with the instant invention.

Finding of prima facie obviousness-rational and motivation (MPEP §2142-2143)

One having ordinary skill in the art would find the claims 37-69 prima facie obvious because one would be motivated to employ the compounds of Svendsen et al. to obtain instant compounds formula (I), wherein the variable m, n, p or q independently represents an integer from 0 to 2 thereof. Dependent claims 38-69 are also rejected along with claim 37 under 35 U.S.C. 103(a).

The motivation to make the claimed processes derived from the known processes of Svendsen et al. would possess similar activity (I.e., pharmaceutical compositions) to that which is claimed in the reference.

Claims Objection

7. Claims 37-69 are objected to as containing non-elected subject matter, i.e., m, n, p, q, heteroaryl or heterocycloalkyl, etc. It is suggested that applicants amend the claims to the scope of the elected subject matter as defined on the pages 2-3 *supra*.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rei-tsang Shiao whose telephone number is (571) 272-0707. The examiner can normally be reached on 8:30 AM - 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/REI-TSANG SHIAO /

Rei-tsang Shiao, Ph.D.
Primary Patent Examiner
Art Unit 1626

September 30, 2008